IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Tarara et al. Application No: 09/851,226 Confirmation No: 4017 Filed: May 8, 2001 Title: PHOSPOLIPID-BASED POWDERS FOR DRUG DELIVERY	Group No: 1617 Examiner: San Ming R. Hui Attorney Docket No: NK 0073.00 Tuesday, December 19, 2006 San Francisco, CA 94107

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

VIA: First Class US Mail

☒ **Appeal Brief (Original)**
☒ **Appeal Brief (Copy of Original (2))**
☒ **Transmittal of Appeal Brief**

Extension of Time

☒ **Applicant petitions for an extension of time under 37 C.F.R. 1.136**

Extension (Months)	Extension Fee	
	Large Entity	Small Entity
☐ One Month	$120.00	$60.00
☐ Two Months	$450.00	$225.00
☐Three Months	$1,020.00	$510.00
☒ **Four Months**	**$1,590.00**	**$795.00**

Total $ 1,590.00

☐ Applicant believes that no extension of term is required. However, this conditional petition is being made in case applicant has inadvertently overlooked the need for a petition for extension of time.

Fees for Extra Claims

	Claims remaining after amendment	Highest number previously paid for	Number Extra	Rate		Additional Fee
				Large Entity	Small Entity	
Total Claims	80	81	0	$50.00	$25.00	$0.00
Independent Claims	7	7	0	$200.00	$100.00	$0.00
Multiple Dependent Claims			0	$360.00	$180.00	$0.00
Supplemental Information Disclosure Statement						
					Total	**$0.00**

Fee Payment

Extension Fees	$1,590.00
Fees for Extra Claims	$.00
Fee for Brief in Support of Appeal	$500.00
Total	**$2,090.00**

☒ **Attached is check no. 2707 in the sum of $2090.00.**
☐Please charge Deposit Account No. _____ in the sum of $120.00.

Fee Deficiency

☒ If any additional extension and/or fee is required, please charge Deposit Account No. 10-0258.
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CERTIFICATE OF TRANSMISSION (37 C.F.R. § 1.8a):

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By: Amy Wells Date: December 19, 2006

Please direct telephone calls to: Ashok K. Janah at (415) 538-1555

Please continue to send correspondence to:

attn: Guy Tucker
Nektar Therapeutics
150 Industrial Road
San Carlos, CA 94070.

Respectfully Submitted,

By: Ashok K. Janah Date: December 19, 2006
Ashok K. Janah
Registration No. 37,487

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weers et al.	Group Art Unit: 1617
Serial No.: 09/851,226	Examiner: San Ming R. Hui
Filed: May 8, 2001	Attorney Docket No: NK 0073.00
For: PHOSPHOLIPID-BASED POWDERS FOR DRUG DELIVERY	December 19, 2006 San Francisco, California

TRANSMITTAL OF APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on June 21, 2006.

This application is on behalf of a large entity.

The Appeal Brief is filed within six months of the Notice of Appeal. Thus, Applicant believes that an extension of time of four months is required. A check in the amount of $2,090.00 is enclosed with this transmittal, to cover the appeal brief filing fee and the extension of time fee.

12/26/2006 BABRAHA1 00000023 09851226
02 FC:1254 1590.00 OP

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By _____ Date December 19, 2006
Amy Wells

Applicant authorizes the Commissioner to charge any other fees associated with this petition to Deposit Account 10-0258.

Should there be any questions, Appellant's representative may be reached at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES
A PROFESSIONAL CORPORATION

Dated: December 19, 2006

By: _____
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weers et al.	Group Art Unit 1617
Serial No: 09/851,226	Examiner: San Ming R. Hui
Filed: May 8, 2001	Attorney Docket No: NK 0073.00
For: PHOSPHOLIPID-BASED POWDERS FOR DRUG DELIVERY	December 19th, 2006 San Francisco, California

APPELLANT'S APPEAL BRIEF (37 C.F.R. § 41.37)

Mail Stop Appeal Brief-Patents
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This brief is in furtherance of the Notice of Appeal filed on June 21, 2006 and is being filed with a petition for a four-month extension. Please charge Deposit Account No. 10-0258 for any required extension fee and appeal brief fee.

12/26/2006 BABRAHA1 00000023 09851226
01 FC:1402 500.00 OP

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By _____ Date December 19, 2006
Amy Wells

TABLE OF CONTENTS

The Brief contains these items under the following headings, and in the order set forth below:

I. REAL PARTY IN INTEREST (§ 41.37 (c)(1)(i))

The real party in interest in this appeal is Nektar Therapeutics, 150 Industrial Road, San Carlos, California 94070.

II. RELATED APPEALS AND INTERFERENCES (§ 41.37 (c)(1)(ii))

There are no other appeals, interferences or judicial proceedings known to appellant, the appellant's legal representative, or assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS (§ 41.37 (c)(1)(iii))

This appeal is taken from the final Office Action mailed on December 21, 2005, in which the Examiner rejected pending claims 1-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65, and 67-99.

On April 20, 2006, Applicant filed a Response to the final Office Action, amending claims and canceling claim 2.

In an Advisory Action mailed on June 26, 2006, the Examiner entered and rejected the pending claims.

Claims 1, 3-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65, and 67-99 are pending in the application. Reconsideration of the present application in view of the arguments and remarks made herein is respectfully requested. All claims filed in Appellant's amendment on April 20, 2006, are on appeal in this case. All the pending claims are presented in the Claims Appendix.

IV. STATUS OF AMENDMENTS (§ 41.37 (c)(1)(iv))

Original Claims 1-52 were filed on May 8, 2001.

After a non-final Office Action in which claims 33-42 were withdrawn from consideration and the rest of the claims were rejected, an amendment was filed on November 25, 2002 and entered by the Examiner, in which claims 6-7 and 33-42 were canceled and claims 53-71 were added.

After a final Office Action in which the claims were rejected, a request for continued examination and an amendment was filed on May 9, 2003 and entered by the Examiner, in which claims 10 and 63 were canceled.

After a non-final Office Action in which the claims were rejected, an amendment was filed on January 26, 2004 and entered by the Examiner, in which claims 16, 56 and 66 were canceled and claims 72-78 were added.

After a final Office Action in which the claims were rejected, a notice of appeal and an amendment was filed on November 5, 2004 and entered by the Examiner in an Advisory Action on December 20, 2004.

A request for continued examination and an amendment was filed on January 5, 2005 and entered by the Examiner, in which claims 79-99 were added.

After a non-final Office Action in which the claims were rejected, an amendment was filed on September 22, 2005 and entered by the Examiner.

After a final Office Action rejecting the claims, an amendment was filed on April 20, 2006 and entered by the Examiner, in which claim 2 was canceled.

The Examiner issued an Advisory Action on June 26, 2006, again rejecting the claims in the previous amendment.

Therefore, the claims on appeal are claims 1, 3-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65, and 67-99 as amended in the amendment dated April 20, 2006, and as presented in the Claims Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER (§ 41.37 (c)(1)(v))

The elements of the claims below have been cited with reference to the Specification of Patent Application Publication No. 20020037316.

Independent claim 1 is to a particulate composition for delivery to the pulmonary system. (Page 9, paragraph 69, lines 1-11.) The composition comprises particles comprising an active agent (Page 5, paragraph 36, lines 1-10) a saturated phospholipid (Page 4, paragraph 30, lines 1-2) and a polyvalent cation (Page 3, paragraph 26, lines 3-6). The molar ratio of polyvalent cation to phospholipid is at least 0.05 (Page 4, paragraph 28, lines 8-10) and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C (Page 2, paragraph 14, lines 1-6 and Pages 3-4, paragraph 26, lines 1-19).

Independent claim 31 is to a particulate composition comprising particles comprising an active agent (Page 5, paragraph 36, lines 1-10), a saturated phospholipid (Page 4, paragraph 30, lines 1-2) and a polyvalent cation (Page 3, paragraph 26, lines 3-6), wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 (Page 4, paragraph 28, lines 8-10). The particles have a gel-to-liquid transition temperature at

least 20°C higher than room temperature. (Page 2, paragraph 14, lines 1-6 and Pages 3-4, paragraph 26, lines 1-19).

Independent claim 32 is to a particulate composition for delivery to the pulmonary system. (Page 9, paragraph 69, lines 1-11.) The composition comprising porous particles comprising 20 – 99.9% of a saturated phospholipid, a polyvalent cation, and 0.1 – 80% active agent. (Page 4, paragraph 30, lines 1-18.) The molar ratio of polyvalent cation to phospholipid is at least 0.05 (Page 4, paragraph 28, lines 8-10) and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C (Page 2, paragraph 14, lines 1-6 and Pages 3-4, paragraph 26, lines 1-19).

Independent claim 44 is to a method of delivering an active agent to a patient in need thereof. The method comprises administering to the respiratory tract of the patient an effective amount of particles comprising an active agent (Page 4, paragraph 30, lines 1-18), a saturated phospholipid (Page 4, paragraph 30, lines 1-2) and a polyvalent cation (Page 3, paragraph 26, lines 3-6). The molar ratio of polyvalent cation to phospholipid is at least 0.05 (Page 4, paragraph 28, lines 8-10) and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C (Page 2, paragraph 14, lines 1-6 and Pages 3-4, paragraph 26, lines 1-19).

Independent claim 59 is to a particulate composition comprising particles comprising a structural matrix comprising a saturated phospholipid (Page 4, paragraph 32, lines 1-10) and a polyvalent cation (Page 3, paragraph 26, lines 3-6). The molar ratio of polyvalent cation to phospholipid is at least 0.05 (Page 4, paragraph 28, lines 8-10) and is sufficiently high to increase the gel-to-liquid crystal transition temperature of

the particles compared to particles without the polyvalent cation, such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C (Page 2, paragraph 14, lines 1-6 and Pages 3-4, paragraph 26, lines 1-19), and wherein the particles further comprise an active agent (Page 4, paragraph 30, lines 1-18).

Independent claim 79 is to a particulate composition for delivery to the pulmonary system. (Page 9, paragraph 69, lines 1-11.) The composition comprises particles comprising an active agent (Page 4, paragraph 30, lines 1-18), a saturated phospholipid (Page 4, paragraph 32, lines 1-10) and a polyvalent cation (Page 3, paragraph 26, lines 3-6). The molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2 (Page 4, paragraph 28, lines 8-10), whereby the gel-to-liquid crystal transition temperature of the particles is higher than particles without the polyvalent cation, and is greater than room temperature by at least 20°C (Page 2, paragraph 14, lines 1-6 and Pages 3-4, paragraph 26, lines 1-19).

Independent claim 90 is to a method of making a temperature stable particulate composition for delivery to the pulmonary system. The method comprises (a) forming a feedstock comprising a saturated phospholipid emulsion and an active agent (Page 8, paragraph 62, lines 1-18); (b) adding a polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2 (Page 4, paragraph 28, lines 8-10); and (c) drying the polyvalent cation containing feedstock to form porous particles (Pages 6-7, paragraph 54, lines 1-10) having a gel-to-liquid crystal transition temperature that is higher than a storage room temperature of the porous particles by at least about 20° C (Page 2, paragraph 14, lines 1-6 and Pages 3-4, paragraph 26, lines 1-19).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL (§ 41.37 (c)(1)(vi))

The grounds of rejection to be reviewed on appeal are as follows:

1. The rejection of claims 1-3, 8-9, 11-15, 17-22, 27-32, 44-55, 59-62, 64-65, and 67- 78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25, 27-30, 34-37 and 41-45 of copending Application No. 09/568,818.

2. The rejection of claims 1-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65, and 67-99 under 35 U.S.C. § 103(a) as being unpatentable over Weers et al. (US 6,309,623) in view of Materne et al. (GB 2065659).

VII. ARGUMENT (§ 41.37 (c)(1)(vii))

1. The rejection of claims 1-3, 8-9, 11-15, 17-22, 27-32, 44-55, 59-62, 64-65, and 67- 78 under the judicially created doctrine of obviousness-type double patenting should be withdrawn as Applicant will file a Terminal Disclaimer.

The Examiner maintained the rejection of claims 1-3, 8-9, 11-15, 17-22, 27-32, 44-55, 59-62, 64-65, and 67-78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25, 27-30, 34-37, 41-45 of copending Application No. 09/568,818.

Applicant has agreed that when the present application or the 09/568,818 application is indicated as allowable, the double patenting issue will be addressed by the filing of a suitable Terminal Disclaimer in the appropriate application. Accordingly, this ground of rejection should be withdrawn.

2. The rejection of claims 1-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65, and 67-99 under 35 U.S.C. § 103(a) as being unpatentable over Weers et al. (US 6,309,623) in view of Materne et al. (GB 2065659) should be reversed.

Applicant respectfully submits that the final Office Action has failed to establish a prima facie obviousness rejection of the claims based on the cited combination of Weers et al. and Materne et al.. To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a), there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of the different references. Second, there must also be a reasonable expectation of success for such a combination. Notably, the prior art references that are combined must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 1

Weers at al. does not teach a particulate composition comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, as claimed in amended claim 1.

Weers et al. teaches selection of a lipid surfactant which already has a gel-to-liquid crystal phase transition temperature of greater than about 40°C, and use of such a surfactant to improve the stability of a respirator dispersion, increase pulmonary

deposition, and facilitate the preparation of the suspension. Specifically, Weers et al. teaches:

> "...in particularly preferred embodiments, the structural matrix is associated with, or comprises, a surfactant such as, a phospholipid or fluorinated surfactant. Although not required, the incorporation of a compatible surfactant can improve the stability of the respiratory dispersions, increase pulmonary deposition, and facilitate the preparation of the suspension."

(Col. 15, line 62 to Col. 16, line 2.) Weers et al. further teaches that particular lipid surfactants should be selected from other lipids to have a gel to liquid crystal phase transition temperature of greater than about 40° C:

> "Lipids, including phospholipids, from both natural and synthetic sources are particularly compatible with the present invention and may be used in varying concentrations to form the structural matrix. Generally, compatible lipids comprise those that have a gel to liquid crystal phase transition greater than about 40° C.

(Col. 16, lines 44-49). Thus, Weers et al. teaches use of surfactant lipids to improve properties of the particles, and teaches that such lipid surfactants should that have a gel to liquid crystal phase transition temperature of greater than about 40°C.

The difference between the teachings of the Weers et al. patent and the instant Specification is explained by the first named inventor of the Weers et al. patent, Dr. Jeffry G. Weers, in paragraphs 9-16 of the attached Declaration (Weers Declaration). This Declaration should be given particular weight because the Declarant is an inventor of both the present application as well as the cited Weers et al. patent.

As explained in the Declaration, Weers et al. teaches that the problem of the low transition temperature of phospholipids is easily solved by selecting only those phospholipids which have high gel to liquid transition temperatures above 40°C. By teaching selection of a phospholipid having a minimum gel to liquid crystal phase

transition temperature of 40°C, the Weers et al. reference teaches away from the more complicated solution of chemically altering a phospholipid with a polyvalent cation to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation to obtain a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, as claimed. If phospholipids having a gel-to-liquid crystal transition temperatures exceeding room temperature by 20°C, for example the 40°C minimum temperature taught by Weers et al., can be easily obtained by simply selecting the right phospholipid, one of ordinary skill in the art would not be motivated to experimentally determine a suitable compound, or a ratio of the same compound to phospholipid to change the gel-to-liquid crystal transition temperature of phospholipid to reach temperatures above room temperature. Selection of the phospholipid having the right minimum temperature should suffice. Thus, Weers at al. would not provide any motivation to one of ordinary skill in the art to try to modify the structure of a phospholipid to obtain a higher gel to liquid transition temperature, because such modification is not taught, or is even taught as unnecessary because it is solved through selection.

In fact, the final Office Action acknowledges that Weers et al. lacks an exemplification of a composition comprising saturated phospholipid and divalent cation. The final Office Action also acknowledges that Weers et al. does not teach the claimed ratio of polyvalent cation to phospholipid of at least 0.05. More importantly, Weers et al. also does not teach or suggest that use of a polyvalent ion in the claimed minimum molar ratios achieves the surprising result of changing its gel-to-liquid transition temperature of a phospholipid. Instead, as acknowledged by the Examiner, Weers et al. teaches that an inorganic salt such as calcium chloride can be added to, for example, to adjust the pH of the feedstock. Weers et al. does not teach or suggest that phospholipid can be chemically modified by a polyvalent cation to have a gel to liquid crystal phase transition temperature that is higher than that of the unmodified phospholipid. Thus the final Office Action is ignoring the language of the claim taken as a whole. Clearly, one of ordinary skill in the art would not have the motivation to devise

the more difficult solution of increasing a gel-to-liquid transition temperature of a particular phospholipid by chemically modifying its structure, when Weers et al. teaches that such a compatibility problem is easily solved simply by selecting a particular phospholipid from commercially available phospholipids.

"In making the assessment of differences between the prior art and the claimed subject matter, section 103 specifically requires consideration of the claimed invention 'as a whole.'" Princeton Biochemicals, Inc. v. Beckman Coulter, Inc. (Fed. Cir., No. 04-1493, 6/9/05). "[S]imply identifying all of the elements in a claim in the prior art does not render a claim obvious. Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275 (Fed. Cir. 2004). Instead section 103 requires some suggestion or motivation in the prior art to make the new combination. In re Rouffet, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998).

Weers et al. does not suggest that a polyvalent cation can be used to increase gel-to-liquid transition temperature of a phospholipid, and does not suggest that such a combination is desirable to achieve a higher gel-to-liquid transition temperature. Nor does Weers et al. teach the claimed molar ratio recited in the present claim, or that ratios above the claimed minimum ratio can increase the gel-to-liquid transition temperature of phospholipid to exceed room temperature by 20°C. Thus, Weers et al. provides no teaching or suggestion to derive the claimed particles as recited in claim 1.

Materne et al. does not make up for the deficiencies of Weers et al. because Materne et al. also does not teach the claimed invention as a whole. Weers et al. provides no teaching or suggestion to one or ordinary skill in the art to seek a reference such as Materne et al.. Further, Materne et al. does not make up for the deficiencies of Weers et al., because Materne et al. does not teach or suggest that a polyvalent ion in the claimed minimum molar ratios of 0.05, when added to phospholipid, achieves the surprising result of forming particles having a gel-to-liquid transition temperature that exceeds room temperature by 20°C.

Materne et al. teaches preparation of calcium phosphatidycholine chloride by the addition of calcium chloride to an unsaturated phospholipid. As explained in paragraphs 17-19 of the Weers Declaration, the description of the physiochemical properties and appearance of the phospholipids taught by Materne et al. corresponds to unsaturated phosphatidylcholines. For example, Materne et al. teaches that phosphatidylcholines are plastic materials of low stability which are difficult to process and handle. Materne et al teaches:

> The eluate is then evaporated giving substantially pure phosphatidylcholine. However, the phosphatidylcholine produced in this manner shows some considerable disadvantages. It is obtained as a plastic material which has low stability and is difficult to further process and handle. Therefore, various efforts have been made to convert this plastic material into a free flowing powder or a liquid of low viscosity by the addition of various auxiliary agents.

(Page 1, lines 36-45.) As explained by Dr. Weers, such a description corresponds to particles of unsaturated phosphatidylcholines which fuse into large conglomerates due to temperature or moisture induced aggregation. (Paragraph 17, Weers Declaration.) In contrast, saturated phosphatidylcholines arrive from vendors as flowable powders which are typically chemically stable because they contain no double bonds that can be oxidized; thus, these materials are not difficult to handle under ambient conditions. Materne et al. further describes the phosphatidylcholines as being yellow in color (see Example 1), which is also indicative of oxidation processes involving double bonds present in unsaturated materials. In contrast, saturated phosphatidylcholines are generally white in appearance. (Paragraphs 18-19, Weers Declaration.)

Furthermore, Materne et al. does not teach a particulate composition comprising particles in which the gel-to-liquid transition temperature is increased to temperatures that exceed room temperature by 20°C, by the addition of a specific molar ration limit of a polyvalent ion to phospholipid. Materne et al. teaches that the calcium

phosphatidylcholine chloride prepared by the described method, is of high purity, can be processed more readily, and has high stability. Materne et al teaches:

> The new calcium phosphatidylcholine chloride which is produced by the present process furthermore may be processed more readily than pure phosphatidylcholine. It is a powder or granular product characterized by a high stability and may be readily used for pharamaceutical preparations in view of its high phosphatidylcholine content.

(Page 1, lines 123-129.) When prepared by the described method, the new calcium phosphatidylcholine chloride is of high purity, can be processed more readily and has high stability. Materne et al further teaches preparation of such a new calcium phosphatidylcholine chloride in Example 1 and then teaches that "[a}fter dissolving the product in choloform and evaporating the product, the product shows unchanged analytical data." (Example 1, page 2, lines 19-35.) Thus, Materne et al, teaches that the calcium addition promotes chemical stability of the product because it does not change when dissolved in various solvents. Materne et al. does not teach a particles in which the gel-to-liquid transition temperature is increased to temperatures that exceed room temperature by 20°C, by the addition of a specific molar ratio limit of a polyvalent ion.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F. 2d 1530, 218 USPQ 871 (Fed. Cir. 1983). The benefits of the claimed invention should be viewed without the benefit of impermissible hindsight vision afforded by the claims themselves.

Materne et al. does not teach the claimed invention as a whole, because Materne et al. does not teach that a ratio of polyvalent cation to phospholipid of at least 0.05 achieves the surprising result of changing the gel-to-liquid transition temperature of particles incorporating the same, to temperatures that exceed room temperature by

20°C. Instead, Materne suggests that calcium addition improves the chemical stability of the composition and not the gel-to-liquid temperature. Furthermore, Materne et al. teaches the use of unsaturated phospholipids and not saturated phospholipids, and provides no motivation for substituting a saturated phospholipid for the described unsaturated phospholipid. Accordingly, there would have been no motivation to substitute the unsaturated phospholipids taught by Materne et al. with the claimed saturated phospholipids. Thus, Materne et al. does not cure the deficiencies of Weers et al., and the cited combination fails to establish a prima facie obviousness rejection.

Furthermore, the surprising and unexpected results of the claimed invention refute the obviousness rejection. The instant claims are to particles comprising saturated phospholipids in combination with a polyvalent cation in a molar ration that increases the gel to liquid transition temperature of the particles. As explained by Dr. Weers, the addition of calcium chloride to a saturated phospholipid as claimed, provides an unexpected increase in gel to liquid crystal transition temperature. (Paragraphs 6-8, Weers Declaration.) The inventive aspect of particles comprising a saturated phospholipid in combination with a polyvalent cation in a particular molar ratio to provide a higher gel to liquid transition temperature is an unexpected result negating the rejection of obviousness. The unexpected increase in Tm of saturated phospholipids, such as DSPC and DDPC, with the addition of polyvalent ion is shown in Tables Ib and Ic below, which are found on page 23-24 of the Specification:

Table Ib (DSPC)

Ca/DSPC (mol/mol)	Tm (°C)
0(hydrated)	58
0	79
0.25	85
0.5	98
1.0	126

Table Ic (DPPC)

Ca/DSPC (mol/mol)	Tm (°C)
0(hydrated)	42
0	63
0.25	69
0.5	89

Furthermore, it is surprising that the addition of a polyvalent ion, such as divalent calcium, would affect the Tm of a phospholipid. It is even more surprising that the addition of a polyvalent cation, for example, in the form of a highly hygroscopic salt such as calcium chloride, would stabilize a dry powder prone to moisture induced destabilization, as one would expect that calcium chloride would readily absorb water and lead to particle aggregation. Figure 1 in the Declaration of Dr. Weers shows a dynamic vapor adsorption (DVS) graph that plots the change in % mass for increasing molar ratio of DSPC to calcium chloride, which shows that unexpectedly, particles containing calcium had about the same moisture absorption properties as particles without calcium. It is believed that as the ratio of amount of calcium polyvalent ion to phospholipid was increased to the claimed 0.5:1 ratio, the polyvalent calcium ion modifies the structure of the phospholipid thereby no longer existing as hydroscopic calcium chloride. It is further believed that the calcium ions intercalate the phospholipids membrane to interact directly with the negatively charged portion of the saturated headgroup of the phospholipid resulting in the dehydration of the head group and condensation of the acryl-chain packing, all of which leads to the increased thermodynamic stability of the phospholipid, as explained at page 8, lines 24-28 of the instant Specification. The unexpected and substantially increase in gel-to-liquid transition temperature of the particles provided numerous benefits including better storage stability of the powders, improved dispersibility, reduced likelihood of absorbing atmospheric water, better lung distribution, and improved emitted dose and fine particle fraction.

Thus, the cited combination of Weers et al. and Materne et al. simply does not sustain a prima facie obviousness rejection of claim 1, which recites a saturated phospholipid, a polyvalent cation, and a molar ratio of the two compounds that is higher than 0.5 to increase the gel to liquid transition temperature of the phospholipid containing particle. For these reasons, claim 1 and its dependent claims are patentable under over Weers et al. and Materne et al..

Claim 31

Claim 31 is to a particulate composition comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and wherein the particles have a gel-to-liquid transition temperature at least 20°C higher than room temperature.

Claim 31 and the claims dependent therefrom, recite that the molar ratio of polyvalent cation to phospholipid is at least 0.05 and that the particles have a gel-to-liquid transition temperature at least 20°C higher than room temperature, and thus, are patentable over Weers et al. and Materne et al. for the same reasons as recited above, and to avoid repetition, will not be repeated.

Claims 32, 44 and 59

Claim 32 is to a particulate composition for delivery to the pulmonary system, the composition comprising porous particles comprising: 20 – 99.9% of a saturated phospholipid; a polyvalent cation; and 0.1 – 80% active agent; wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

Claim 44 is to a method of delivering an active agent to a patient in need thereof, the method comprising administering to the respiratory tract of the patient an effective amount of particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such

that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

Claim 59 is to a particulate composition comprising particles comprising a structural matrix comprising a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, and to obtain particles having a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, and wherein the particles further comprise an active agent.

Claims 32, 44 and 59, and the claims dependent therefrom, all recite inter alia, that the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, and thus, are patentable over Weers et al. and Materne et al. for the same reasons as recited above.

Claims 72-78

Claims 72-78 are further patentable over Weers et al. and Materne et al., because the cited references do not teach a particulate composition comprising a saturated, zwitterionic phospholipid as taught in claims 72-74, 77, and 78, nor do the cited references teach hollow particles as claimed in claim 76. For these reasons, claims 72-78 are independently allowable over the cited references.

Claim 79

Claim 79 is to a particulate composition for delivery to the pulmonary system, the composition comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2, whereby the gel-to-liquid crystal transition temperature of the particles is higher than particles without the polyvalent cation, and is greater than room temperature by at least 20°C.

Claim 79, and the claims dependent therefrom, are patentable over Weers et al. and Materne et al., because the cited references do not teach a molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2, whereby the gel-to-liquid crystal transition temperature of the particles is higher than particles without the polyvalent cation, and is greater than room temperature by at least 20°C. The reasons and arguments supporting the same are recited above.

Claim 90

Claim 90 is to a method of making a temperature stable particulate composition for delivery to the pulmonary system, the method comprising: forming a feedstock comprising a saturated phospholipid emulsion and an active agent; adding a polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2; and drying the polyvalent cation containing feedstock to form porous particles having a gel-to-liquid crystal transition temperature that is higher than a storage room temperature of the porous particles by at least about 20° C.

Claim 90, and the claims dependent therefrom, are also patentable over the cited references because the references do not teach a method of making a temperature stable particulate composition comprising the step of adding a polyvalent

cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2, and drying the polyvalent cation containing feedstock to form porous particles having a gel-to-liquid crystal transition temperature that is higher than a storage room temperature of the porous particles by at least about 20° C.

3. CONCLUSION

For the foregoing reasons, the rejections under 35 U.S.C. §103(a) should be reversed by the Board, and all of the claims presented should be allowed.

Respectfully submitted,

JANAH & ASSOCIATES
A PROFESSIONAL CORPORATION

Date: December 19, 2006

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VIII. CLAIMS APPENDIX (37 C.F.R. § 41.37(c)(1)(viii))

The text of the claims involved in the appeal are:

1. A particulate composition for delivery to the pulmonary system, the composition comprising:

particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

2. (Canceled)

3. A particulate composition according to claim 1 wherein said gel-to-liquid crystal transition temperature is greater than room temperature by at least 40°C.

4. A particulate composition according to claim 1 further comprising a surfactant selected from the group consisting of nonionic detergents, nonionic block copolymers, ionic surfactants and combinations thereof.

5. A particulate composition according to claim 4 wherein the surfactant is selected from the group consisting of sorbitan esters, ethoxylated sorbitan esters, fatty acids, salts, sugar esters, ethylene oxides, and combinations thereof.

6-7. (Canceled)

8. A particulate composition according to claim 1 wherein the polyvalent cation is a divalent cation.

9. A particulate composition according to claim 8 wherein the divalent cation is selected from the group consisting of calcium, magnesium and zinc.

10. (Canceled)

11. A particulate composition according to claim 8 wherein the molar ratio of divalent cation to phospholipid is 0.05 – 2.0.

12. A particulate composition according to claim 8 wherein the molar ratio of divalent cation to phospholipid is 0.25 – 1.0.

13. A particulate composition according to claim 12 wherein the divalent cation is calcium.

14. A particulate composition according to claim 13 wherein the molar ratio of calcium to phospholipid is about 0.50.

15. A particulate composition according to claim 1 wherein the phospholipid comprises a natural or synthetic lung surfactant.

16. (Canceled)

17. A particulate composition according to claim 1 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol, and salts thereof.

18. A particulate composition according to claim 1 further comprising a polymer selected from the group consisting of polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone, polylactides, polyglycolides, polyethylene glycol, and mixtures thereof.

19. A particulate composition according to claim 1 comprising particles having a mass median diameter of less than 20 microns.

20. A particulate composition according to claim 19 wherein the mass median diameter is within 0.5 – 5 microns.

21. A particulate composition according to claim 19 wherein the particles comprise an aerodynamic diameter of less than 10 microns.

22. A particulate composition according to claim 21 wherein the aerodynamic diameter is within 0.5 – 5 microns.

23. A particulate composition according to claim 1 comprising an emitted dose of at least 40%.

24. A particulate composition according to claim 1 comprising an emitted dose of at least 60%.

25. A particulate composition according to claim 1 comprising an emitted dose of at least 90%.

26. A particulate composition according to claim 1 further comprising a non-aqueous suspension medium.

27. A particulate composition according to claim 1 further comprising an excipient selected from the group consisting of amino acids, carbohydrates, inorganic salts, organic salts, carboxylic acids, and mixtures thereof.

28. A particulate composition according to claim 27 wherein the excipient is selected from the group consisting of hydrophobic amino acids, monosaccharides, disaccharides, polysaccharides, sodium citrate, citric acid, ammonium carbonate, ammonium acetate, and ammonium chloride.

29. A particulate composition according to claim 1 wherein the bulk density of the particulate composition is less than 0.5 g/cm^3.

30. A particulate composition according to claim 29 wherein the bulk density of the particulate composition is less than 0.05 g/cm^3.

31. A particulate composition comprising:

particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and wherein the particles have a gel-to-liquid transition temperature at least 20°C higher than room temperature.

32. A particulate composition for delivery to the pulmonary system, the composition comprising porous particles comprising:

20 – 99.9% of a saturated phospholipid;

a polyvalent cation; and

0.1 – 80% active agent;

wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

33-43. (Canceled)

44. A method of delivering an active agent to a patient in need thereof, the method comprising:

administering to the respiratory tract of the patient an effective amount of particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

45. A method according to claim 44 wherein the particulate composition comprises particles having a mass median diameter of less than 20 microns.

46. A method according to claim 45 wherein the mass median diameter is within 0.5 – 5 microns.

47. A method according to claim 45 wherein the particles comprise an aerodynamic diameter of less than 10 microns.

48. A method according to claim 47 wherein the aerodynamic diameter is within 0.5 – 5 microns.

49. A method according to claim 44 wherein the particles comprise polyvalent cation at a molar ratio of polyvalent cation: phospholipid of 0.25-1.0.

50. A method according to claim 49 wherein the polyvalent cation comprises calcium.

51. A method according to claim 48 wherein the particles comprise a bulk density of less than 0.5 g/cm^3.

52. A method according to claim 51 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol, and salts thereof.

53. A particulate composition according to claim 1 wherein the particles are hollow and porous.

54. A particulate composition according to claim 1 comprising 0.1 – 80% w/w of the active agent.

55. A particulate composition according to claim 31 wherein the particles are hollow and porous.

56. (Canceled)

57. A particulate composition according to claim 31 wherein the gel-to-liquid transition temperature is at least 40°C higher than room temperature.

58. A particulate composition according to claim 31 wherein the phospholipid is selected from dipalmitoylphosphatidylcholine or distearoylphosphatidylcholine.

59. A particulate composition comprising:

particles comprising a structural matrix comprising a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, and wherein the particles further comprise an active agent.

60. A particulate composition according to claim 59 wherein the phospholipid comprises dipalmitoylphosphatidylcholine or distearoylphosphatidylcholine.

61. A particulate composition according to claim 59 wherein the polyvalent cation is a divalent cation.

62. A particulate composition according to claim 61 wherein the divalent cation is selected from the group consisting of calcium, magnesium, and zinc.

63. (Canceled)

64. A particulate composition according to claim 59 wherein the molar ratio of polyvalent cation to phospholipid is 0.05 – 2.0.

65. A particulate composition according to claim 59 wherein the molar ratio of polyvalent cation to phospholipid is 0.25 – 1.0.

66. (Canceled)

67. A particulate composition according to claim 59 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol, and salts thereof.

68. A particulate composition according to claim 61 wherein the divalent cation is calcium.

69. A particulate composition according to claim 68 wherein the molar ratio of calcium to phospholipid is about 0.50.

70. A particulate composition according to claim 59 wherein the composition has a gel-to-liquid crystal transition temperature at least 20°C higher than room temperature.

71. A particulate composition according to claim 59 wherein the composition has a gel-to-liquid crystal transition temperature at least 40°C higher than room temperature.

72. A particulate composition according to claim 1 wherein the saturated phospholipid is a saturated, zwitterionic phospholipid.

73. A particulate composition according to claim 31 wherein the saturated phospholipid is a zwitterionic phospholipid.

74. A particulate composition according to claim 32 wherein the saturated phospholipid is a zwitterionic phospholipid.

75. A particulate composition according to claim 32 wherein the molar ratio of polyvalent cation to phospholipid is effective to increase the gel to liquid crystal transition temperature of the particles compared to particles without the polyvalent cation.

76. A particulate composition according to claim 32 wherein the particles are hollow.

77. A method according to claim 44 wherein the saturated phospholipid is a saturated zwitterionic phospholipid.

78. A particulate composition according to claim 59 wherein the saturated phospholipid is a saturated, zwitterionic phospholipid.

79. A particulate composition for delivery to the pulmonary system, the composition comprising:

particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2, whereby the gel-to-liquid crystal transition temperature of the particles is higher than particles without the polyvalent cation, and is greater than room temperature by at least 20°C.

80. A particulate composition according to claim 79 wherein the molar ratio of divalent cation to phospholipid is from 0.25 to 1.

81. A particulate composition according to claim 79 wherein the polyvalent cation is a divalent cation.

82. A particulate composition according to claim 81 wherein the divalent cation is selected from the group consisting of calcium, magnesium and zinc.

83. A particulate composition according to claim 81 wherein the divalent cation is calcium.

84. A particulate composition according to claim 83 wherein the molar ratio of calcium to phospholipid is about 0.50.

85. A particulate composition according to claim 79 wherein the gel-to-liquid crystal transition temperature is greater than a storage temperature for the particulate composition by at least 20°C.

86. A particulate composition according to claim 79 further comprising a surfactant selected from the group consisting of nonionic detergents, nonionic block copolymers, ionic surfactants and combinations thereof.

87. A particulate composition according to claim 79 wherein the particles have a mass median diameter of less than 20 microns and an aerodynamic diameter of less than 10 microns.

88. A particulate composition according to claim 79 further comprising an excipient selected from the group consisting of amino acids, carbohydrates, inorganic salts, organic salts, carboxylic acids, and mixtures thereof.

89. A particulate composition according to claim 79 wherein the bulk density of the particulate composition is less than 0.5 g/cm^3.

90. A method of making a temperature stable particulate composition for delivery to the pulmonary system, the method comprising:

(a) forming a feedstock comprising a saturated phospholipid emulsion and an active agent;

(b) adding a polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2; and

(c) drying the polyvalent cation containing feedstock to form porous particles having a gel-to-liquid crystal transition temperature that is higher than a storage room temperature of the porous particles by at least about 20° C.

91. A method according to claim 90 wherein (b) comprises adding the polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is from 0.25 to 1.

92. A method according to claim 90 wherein the polyvalent cation is a divalent cation.

93. A method according to claim 92 wherein the divalent cation is selected from the group consisting of calcium, magnesium and zinc.

94. A method according to claim 92 wherein the divalent cation is calcium.

95. A method according to claim 90 further comprising adding to the feedstock, a surfactant selected comprising nonionic detergents, nonionic block copolymers, ionic surfactants and combinations thereof.

96. A method according to claim 90 further comprising adding to the feedstock a polymer selected from the group consisting of polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone, polylactides, polyglycolides, polyethylene glycol, and mixtures thereof.

97. A method according to claim 90 comprising drying the polyvalent ion comprising feedstock wherein the particles have a mass median diameter of less than 20 microns and an aerodynamic diameter of less than 10 microns.

98. A method according to claim 90 comprising adding an excipient to the feedstock, the excipient comprising amino acids, carbohydrates, inorganic salts, organic salts, carboxylic acids, and mixtures thereof.

99. A method according to claim 90 comprising drying the polyvalent cation comprising feedstock to provide a bulk density of the porous particles that is less than 0.5 g/cm^3.

IX. EVIDENCE APPENDIX (§ 41.37(c)(1)(ix))

Please see attached Declaration of Dr. Jeffrey G. Weers under 37 C.F.R. § 1.132.

X. RELATED PROCEEDINGS APPENDIX (§ 41.37(c)(1)(x))

None.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weers et al. Application No: 09/851,226 Confirmation No: 4017 Filed: May 8, 2001 Title: PHOSPHOLIPID-BASED POWDERS FOR DRUG DELIVERY	Group Art Unit: 1617 Examiner: HUI, San Ming Jr. Attorney Docket No: NK.73.US September 8, 2005 San Francisco, California

DECLARATION OF DR. JEFFRY G. WEERS UNDER 37 C.F.R. § 1.132

I, Jeffry G. Weers, hereby declare:

1. I am a co-inventor the instant application and I currently employed by Nektar Therapeutics Inc. in the position of Senior Director, Product Development, at NEKTAR THERAPEUTICS, INC. the assignee of the present application.

2. I have a Ph.D. in Physical Chemistry from the University of California, Davis, California, and a B.S., Honors in Chemistry, University of Puget Sound, Tacoma, Washington. I have over 20 years of experience in the research and development of colloids and the use of polymers and surfactants in drug delivery. I am an inventor in numerous patents, have publications in refereed journals, and have been an invited presentor at scientific conferences. I am currently Section Editor and on the Editorial Board of the journal Current Opinion in Colloid & Interface Science and Guest Editor for Colloids and Surfaces. I have attached hereto a copy of my curriculum vitae which demonstrates that I am an expert in the field of aerosolized medications and have particular knowledge and understanding of the formulation and processing challenges in developing phospholipid compositions of sufficient physical and chemical stability to be suitable for formulating as spray dried powders intended for administration via inhalation.

3. I have reviewed the above-identified patent application, the claims being presented by amendment, the office actions which have been entered in this case, and the references relied upon by the Examiner.

4. It is my opinion that the invention, as claimed, would not have been obvious to one of ordinary skill in the art over any combination of references cited by the Examiner and any other combination of references of which I am aware due to the unexpected benefits increasing the physical stability and dispersibility of the particles comprising saturated phospholipid and a polyvalent cation, the molar ratio of polyvalent cation to phospholipid being at least 0.05 and sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation.

5. As explained in the Specification of the present patent application, phospholipids are especially difficult to formulate as dry powders as their low gel to liquid transition temperature (Tm) values and amorphous nature lead to powders which are very sticky and difficult to deaggregate and aerosolize. The gel to liquid transition temperatures of the phospholipids are critical to obtaining phospholipids-based powders that both flow well and are readily dispersible from a dry powder device.

6. We discovered that polyvalent cations unexpectedly substantially increase the Tm of saturated phospholipids, providing numerous benefits including better storage stability of the powders, improved dispersibility, reduced likelihood of absorbing atmospheric water, better lung distribution, and improved emitted dose and fine particle fraction. The unexpected increase in Tm of saturated phospholipids such as DSPC and DDPC, when polyvalent ion is added in the molar ratios of 0.25 to 1, is shown in Tables I and II below:

Table I (DSPC)

Ca/DSPC (mol/mol)	Tm (°C)
0	79
0.25	85
0.5	98
1.0	126

Table II (DPPC)

Ca/DSPC (mol/mol)	Tm (°C)
0	63
0.25	69
0.5	89

7. It is surprising that the addition of a polyvalent ion, such as divalent calcium, would affect the Tm of the phospholipids at all. We believe that the calcium ions intercalate the phospholipids membrane to interact directly with the negatively charged portion of the

saturated headgroup of the phospholipid resulting in the dehydration of the head group and condensation of the acryl-chain packing, all of which leads to the increased thermodynamic stability of the phospholipid, as explained at page 8, lines 24-28 of the instant Specification.

8. It is further surprising that the addition of a polyvalent cation, for example, in the form of a highly hygroscopic salt such as calcium chloride, would stabilize a dry powder prone to moisture induced destabilization, as one would expect that salts such as calcium chloride would readily pick up water leading to particle aggregation. Figure 1 shows a dynamic vapor adsorption (DVS) graph that plots the change in %mass for increasing molar ratio of DSPC to calcium chloride. As the ratio of amount of calcium polyvalent ion to phospholipid was increased to a about 2:1 (which is the reverse of, but corresponds to, the claimed 0.5:1 ratio of saturated phospholipid to polyvalent cation), unexpectedly, the resultant spray dried particle had about the same moisture absorption properties. It would be expected that the addition of calcium chloride, which is hygroscopic and absorbs water from the atmosphere, would increase the moisture absorption properties of phospholipid; however, it does not do so because the polyvalent calcium ion modifies the structure of the phospholipid thereby no longer existing as hydroscopic calcium chloride.

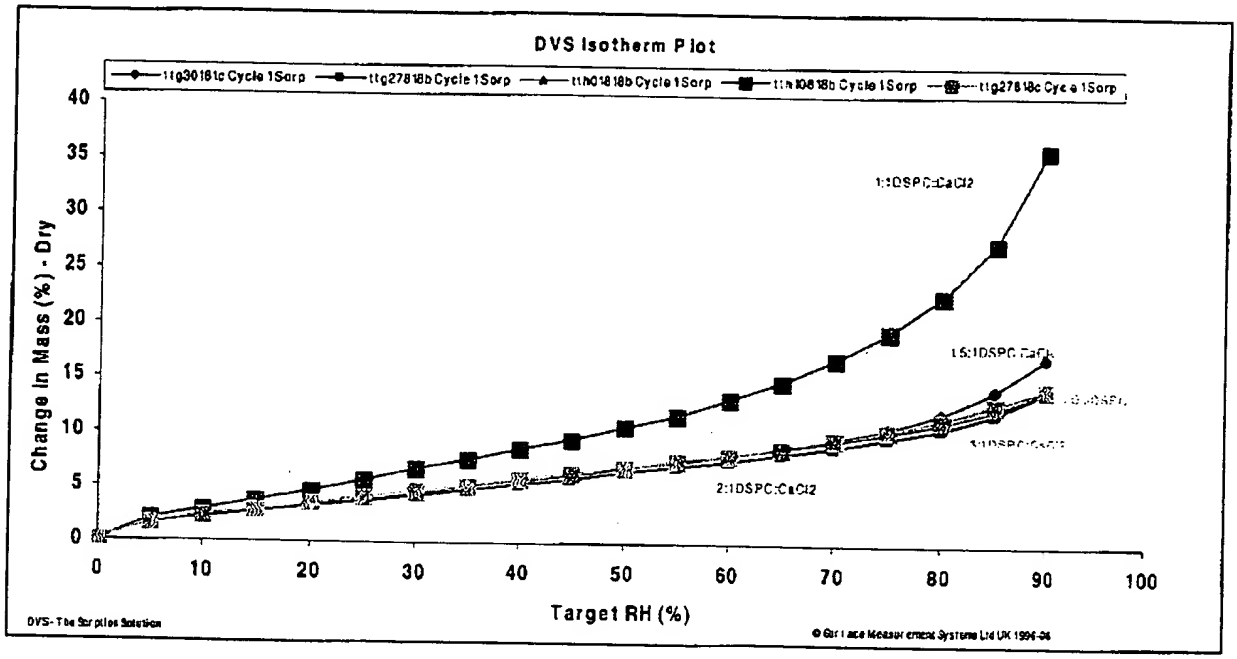


Figure 1.

9. In making the obviousness rejections, the Examiner relies heavily upon the teachings of a patent of which I am the first named inventor, U.S. patent no. 6,309,623 to Weers et al..

10. However, the Weers et al. patent does not teach particles comprising an active agent, a saturated phospholipid and a polyvalent cation, in which the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, as claimed in claim 2 of the instant patent application.

11. Instead, in the Weers et al. patent, we teach particles having a structural matrix that comprising a surfactant such as a phospholipid which has a preselected, naturally occurring, gel to liquid crystal phase transition temperatures. We specifically teach preselecting lipids "that have a gel to liquid crystal phase transition greater than about 40°C." (Weers et al., Column 16, lines 44-49). Thus, in the Weers et al. patent, we teach the selection of lipid surfactants that have a particular gel to liquid transition temperature.

12. However, in the Weers et al. patent, we do not teach chemically modifying phospholipid by a polyvalent cation in a selected molar ratio to change the structure of the phospholipid to obtain a new phospholipid having a gel to liquid transition temperature that is higher than that of the unmodified phospholipid.

13. In other words, Weers et al. teaches that the problem of the excessive low Tm of phospholipids is easily solved by selecting only those phospholipids which have high gel to liquid transition temperatures above 40°C. Thus, Weers at al. would not provide any motivation to one of ordinary skill in the art to try to modify the structure of a phospholipid to obtain a higher gel to liquid transition temperature, because such modification is not taught, or is even taught as unnecessary because it is solved through selection.

14. The Examiner acknowledges that "Weers et al. lacks an exemplification of a composition comprising saturated phospholipid and divalent cation, and a teaching of the ratio of cation to phospholipid." But, further, in Weers et al. we simply do not teach or suggest the claimed solution of chemically altering a saturated phospholipid to provide an increased gel to liquid crystal phase transition temperature.

15. Nor do we teach in Weers et al. that a chemical capable of chemically modifying a saturated phospholipid to achieve a higher Tm is a polyvalent cation. Instead in Weers et al. we only mention calcium chloride, in the context of "optional components that may include conventional viscosity modifiers, buffers such as phosphate buffers or other conventional biocompatible buffers or pH adjusting agents such as acids or bases...." The calcium chloride recited in Weers et al. is only taught as an example of a suitable acidic or basic salt to modify pH etc., but not as a Tm modifier for a phospholipid.

16. Further, in Weers et al. we do not teach that a molar ratio of polyvalent cation of greater than 0.5 is needed to modify the phospholipid to achieve a higher Tm. Nor do we teach the desirability of selecting a particular molar ratio of polyvalent ion that can change the structure of the phospholipid to obtain a new structure having a gel to liquid transition temperature that is higher than that of the unmodified phospholipid. In fact, no molar ratios of cation to phospholipid are taught at all in Weers et al.

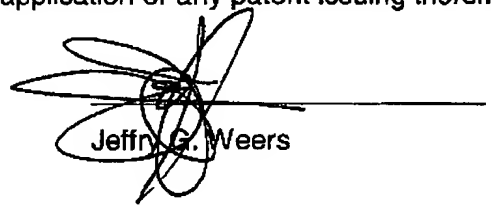
17. Furthermore, the instant claims are to a saturated phospholipid with added polyvalent ion which is not taught by the combination of Weers et al. and Materne et al.. Materne et al. describes the use of calcium chloride only in combination with unsaturated phosphatidylcholine. Although not explicitly stated in Materne, it is clear to one of ordinary skill in the art that the phosphatidylcholines described by Materne et al. are unsaturated because of their physicochemical properties and appearance. Specifically, Materne et al. teaches that the phosphatidylcholines as plastic materials of low stability, which are difficult to process and handle. This is an accurate description of unsaturated phosphatidylcholines with a Tm<10 °C, in which the particles often fuse into large agglomerates due to temperature or moisture induced aggregation. Unsaturated phosphatidylcholines are also unstable due to oxidative processes involving the double bonds and must typically be stored at -20°C to maintain stability.

18. Furthermore, Materne describes phosphatidylcholines which have a yellow color. This yellow color is typically a result of oxidative processes involving the double bond presented in unsaturated materials; further evidencing that the taught phospholipids are not saturated. The phosphatidylcholines taught by Materne et al. are intended for use in preparing phosphatidylcholines raw material and not as a final pharmaceutical product where the physical properties of the lipids are much more demanding.

19. In contrast, the claimed saturated phospholipids are flowable powders in their natural state which are stable chemically since they contain no double bonds that can be oxidized. Further, saturated phospholipids such as saturated phosphatidylcholines are not difficult to handle under normal ambient conditions. Saturated phosphatidylcholines are also typically white in appearance, not yellow.

20. For these reasons, the combination of Weers et al. and Materne et al. simply do not teach the claimed subject matter comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, as claimed in claim 2 of the instant patent application.

21. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.



Jeffry G. Weers

8-Sep-05

Date